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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,448	11/07/2001	David Lewis	Mirus.030.03	3784

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,448	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003 and 25 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-16* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *December 16, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed December 16, 2003 and March 25, 2004.

Claim 2 has been canceled. Claims 1, 3, 8 have been amended.

Claims 1 and 3-16 are pending in the instant application.

Information Disclosure Statement

Applicants Information Disclosure Statement, filed December 16, 2003 is acknowledged. The reference referred to therein has been considered on the merits.

Response to Amendment

Applicants Amendment, filed March 25, 2004, to recite, "A process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression" as recited in the originally filed claim 1, is acknowledged.

Applicants Amendment and Declaration filed under 37 C.F.R. §1.132, filed December 16, 2003, are acknowledged. It is noted that the Declaration filed under 37 C.F.R. §1.132 appears to be a total of 21 pages, however, page 10 appears to be duplicated and page 19 appears to be missing. Applicants Declaration filed under 37 C.F.R. §1.132 has been fully considered.

In the Amendment filed December 16, 2003, Applicants have amended the Specification to become a CIP from earlier filed applications. Specifically, this application has been amended

to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13, 1995, now abandoned.

Applicants attention is directed to 37 C.F.R. §1.78(a)(2) where it states that benefit claims under 35 U.S.C. 119(e), 120, 121, and 365(c) must be made during the pendency of the application and **within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application**. In the instant case, neither condition has been met, and therefore, Applicant must file a petition for an unintentionally delayed claim, pay a surcharge under 37 C.F.R. 1.17(t), and provide a statement that the entire delay between the date the claim was due under 37 C.F.R. §1.78(a)(2) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. See 37 C.F.R. §1.78(a)(3). Accordingly, the instantly claimed invention has not been given priority back to the filing date of the parent applications.

It is also noted that Applicants have amended the Specification to become a CIP from earlier filed applications. Specifically, this application has been amended to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13,

1995, now abandoned. When comparing the instant specification with the parent specification, USSN 08/571,536, does not have appear to have support for claims 10, 11, and 12, drawn to a process for delivering a dsRNA or siRNA into a cell of a mammal to inhibit protein expression. Further, parent application 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, does not have appear to have support for claims 10, 11, and 12. Similarly, parent applications 09/391,260, filed September 7, 1999, now abandoned, and 09/707,117 do not appear to have support for claims 10, 11, and 12. Therefore, claims 10, 11, and 12, drawn to a process for delivering a dsRNA or siRNA into a cell of a mammal to inhibit protein expression have not been given priority to the parent applications, but instead have been awarded priority of the filing date of the instant application, November 7, 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "wherein the nucleic acid expression is inhibited" in (d). There is insufficient antecedent basis for this limitation in the claim because the claim preamble refers to inhibiting protein expression, not nucleic acid expression. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

In the previous Office Action filed October 6, 2003, claim 8 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 was indefinite because it recited the limitation "the parenchymal cell" in line 1. There was insufficient antecedent basis for this limitation in the claim because claim 1, from which claim 8 depends, makes reference to "a cell" not a "parenchymal cell".

This rejection is withdrawn in view of Applicants amendment to the claim to correct for lack of antecedent basis, filed December 16, 2003.

In the previous Office Action filed October 6, 2003, claims 1 and 3-16 were rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a process for mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA into a cell of a mammal to inhibit protein expression, does not reasonably provide enablement for a process for delivering any polynucleotide into any cell of a mammal to inhibit protein expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This rejection is withdrawn in view of Applicants arguments and Declaration filed under 37 C.F.R. §1.132, filed December 16, 2003. More specifically, Applicants arguments, Example 11 of the instant specification, and the demonstrations of inhibition of endogenous genes by tail vein delivery of naked siRNA in mice (see Declaration pages 1-4, 7-9, and 10) were considered persuasive to obviate the scope of enablement rejection of record.

Double Patenting

In the previous Office Action filed October 6, 2003, claims 1, 3-5, 8, 13, and 15 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1, 2, 6, 7, and 8 of U. S. Patent No. 6,379,966 ('966). It is noted that claim 16 was inadvertently not included in this rejection, but was intended to be included in the rejection. Therefore, claim 16 is also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1, 2, 6, 7, and 8 of U. S. Patent No. 6,379,966 ('966). Although the conflicting claims are not identical, they are not patentably distinct from each other because a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression comprising inserting the polynucleotide into a vessel in a mammal, wherein vessel permeability is increased by increasing pressure against vessel walls, wherein increasing the pressure consists of increasing a volume, wherein increasing the volume consists of inserting the polynucleotide in solution in the vessel, and wherein the cell is a liver cell as instantly claimed is encompassed in the process for delivering a polynucleotide complexed with a compound into a extravascular parencymal cell of a mammal comprising inserting the

polynucleotide into a mammalian blood vessel, increasing permeability of the blood vessel, wherein increasing the permeability consists of increasing pressure against the blood vessel walls, wherein increasing the pressure consists of increasing a volume of fluid within the vessel as recited in ('966).

This rejection is maintained for the reasons of record set forth in the previous Office Action, filed October 6, 2003.

In response to this rejection, Applicants argue that the application has been amended to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13, 1995, now abandoned, and therefore the double patenting rejection is obviated.

Applicant's arguments have been considered but are not found persuasive because amending the instant application to claim benefit of a parent application(s) cannot obviate a double patenting rejection. Regardless of the priority of the instant application, the double patenting rejection is applicable because the nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438,

164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Therefore the double patenting rejection against claims 1, 3-5, 8, 13, 15, and 16 is not obviated and is maintained.

Applicant is also reminded that the instant application has not met the conditions of 37 C.F.R. §1.78(a)(2) – time period for making a claim for benefit, and therefore the instantly claimed invention has not been given priority back to the filing date of the parent applications (for further explanation, see Response to Amendment above).

Claim Rejections - 35 USC § 102

In the previous Office Action filed October 6, 2003, claims 1, 3-6, 8, 13, and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Makino et al. (Hypertension, 1998 Vol. 31:1166-1170). It is noted that claim 16 was inadvertently not included in this rejection, but was intended to be included in the rejection. Therefore, claim 16 is also rejected under 35 U.S.C. 102(b) as being anticipated by Makino et al. (Hypertension, 1998 Vol. 31:1166-1170).

Claim 1 is drawn to a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression, comprising making a polynucleotide that is complementary to a nucleic acid sequence, inserting the polynucleotide into a vessel and delivering the

polynucleotide to the cell. Claims 2-6, 8, 13, 15, and 16 are dependent on claim 1 and include all the limitations of claim 1 and provide the further limitations, wherein vessel permeability is increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, wherein the vessel consists of a tail vein and wherein the cell is a liver cell and wherein the pressure increases extravascular volume.

Makino et al. disclose the intravenous injection with antisense oligodeoxynucleotides against angiotensinogen into SHR via the tail vein (see Abstract). Makino et al. further disclose the synthetic oligonucleotides were purified, dried, and resuspended in Tris-EDTA. Asialoglycoprotein-poly(L)lysine was then added to the oligonucleotides with vigorous mixing. This solution was incubated, dialyzed against saline, filtered and electrophoresed through 2% agarose. Those antisense oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine retained in the well were intravenously injected via the tail vein (see page 1167, first column, for example). Makino et al. further disclose that after intravenous injection of oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine, mRNA levels of angiotensinogen were decreased from liver tissues specimens (see Figure 5).

The term "vessel" is interpreted broadly such that administering the oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine via tail vein is equivalent to inserting the polynucleotide into a vessel as claimed. Injection into the tail vein with oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine is equivalent to increasing vessel permeability, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of intravascular injection would inherently increase pressure in the area of injection and at the time

of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the tail vein. The oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine administered via tail vein of Makino et al. reached the liver because asialoglycoprotein-poly(L)lysine are carrier molecules targeted to the liver and the use of this carrier molecule can be successfully used to regulate liver gene expression (see page 1166, second column, for example and Figure 5).

Thus, Makino et al. anticipate claims 1, 3-6, 8, 13, 15, and 16.

This rejection is maintained for the reasons of record set forth in the previous Office Action, filed October 6, 2003.

In response to this rejection, Applicants argue that the application has been amended to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13, 1995, now abandoned. Applicants contend that the current application becomes a Continuation-In-Part of the originally 1995 filing based upon use of its vascular delivery processes, and therefore the 35 U.S.C. 102(b) art rejection is obviated.

Applicants arguments have been considered but are not found persuasive because as discussed above, the instant application has not met the conditions of 37 C.F.R. §1.78(a)(2) – time period for making a claim for benefit, and therefore the instantly claimed invention has not been given priority back to the filing date of the parent applications (for further explanation, see

Response to Amendment above). Therefore the 35 U.S.C. 102(b) art rejection, as being anticipated by Makino et al., is not obviated and is maintained.

In the previous Office Action filed October 6, 2003, claims 1, 3-5, 9, 10, 13, 14, and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Wianny et al. (Nature Cell Biology, 2000 Vol. 2:70-75).

Wianny et al. disclose long dsRNAs diluted in water and microinjected into the cytoplasm of oocytes and embryos of mice (see page 74, first and second columns, for example). Wianny et al. further disclose that some blastocytes derived from zygotes injected with dsRNAs were transferred into the uteri of pseudopregnant mice (see page 74, second column, for example and page 72, first column).

The term "vessel" is interpreted broadly such that transferring the zygotes injected with dsRNA into the uteri is equivalent to inserting the polynucleotide into a vessel as claimed. Transferring the zygotes injected with dsRNA into the uteri is equivalent to increasing vessel permeability, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, increasing extravascular volume, and organ volume as claimed because the method of transferring the zygotes injected with dsRNA into the uteri would inherently increase pressure in the area of microinjection and at the time of transferring. The pressure against the vessel walls would inherently be increased because the microinjection needle used is external to the uteri and injecting an increased volume of solution into the uteri would increase volume and pressure against the vessel walls.

Thus, Wianny et al. anticipate claims 1, 3-5, 9, 10, 13, 14, and 15.

This rejection is maintained for the reasons of record set forth in the previous Office Action, filed October 6, 2003.

In response to this rejection, Applicants argue that the application has been amended to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13, 1995, now abandoned. Applicants contend that the current application becomes a Continuation-In-Part of the originally 1995 filing based upon use of its vascular delivery processes, and therefore the 35 U.S.C. 102(b) art rejection is obviated.

Applicants arguments have been considered but are not found persuasive because as discussed above, the instant application has not met the conditions of 37 C.F.R. §1.78(a)(2) – time period for making a claim for benefit, and therefore the instantly claimed invention has not been given priority back to the filing date of the parent applications (for further explanation, see Response to Amendment above). Therefore the 35 U.S.C. 102(b) art rejection, as being anticipated by Wianny et al., is not obviated and is maintained.

It is also noted that Applicants have amended the Specification to become a CIP from earlier filed applications. Specifically, this application has been amended to claim benefit of provisional applications 60/315,934, filed August 27, 2001, and 60/324,155, filed September 20, 2001; and is a Continuation-in-Part of applications 09/707,117, filed November 6, 2000 and 09/391,260, filed September 7, 1999, which is a Continuation of 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, which is a continuation of 08/517,536, filed December 13,

1995, now abandoned. When comparing the instant specification with the parent specification, USSN 08/571,536, does not have appear to have support for claim 10 drawn to a process for delivering a dsRNA into a cell of a mammal to inhibit protein expression. Further, parent application 08/975,573, filed November 21, 1997, now US Patent No. 6,265,387, does not have appear to have support for claim. Similarly, parent applications 09/391,260, filed September 7, 1999, now abandoned, and 09/707,117 do not appear to have support for claim 10. Therefore, claim 10, drawn to a process for delivering a dsRNA into a cell of a mammal to inhibit protein expression have not been given priority to the parent applications, but instead have been awarded priority of the filing of the instant application, November 7, 2001.

Thus, Wianny et al. anticipate claims 1, 3-5, 9, 10, 13, 14, and 15.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al.[U.S. Patent No. 6,107,027].

Claim 1 is drawn to a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression, comprising making a polynucleotide that is complementary to a

nucleic acid sequence, inserting the polynucleotide into a vessel and delivering the polynucleotide to the cell. Claim 7 is dependent on claim 1 and includes all the limitations of claim 1 and provides the further limitation, wherein the vessel consists of a bile duct.

Kay et al. disclose a method for inhibiting hepatitis C virus RNA in cells comprising administering an adenovirus encoding a ribozyme, which inhibits the hepatitis C virus (see claim 1). Kay et al. further disclose the adenovirus encoding a ribozyme, which inhibits the hepatitis C virus, is infused via the bile duct (see claim 7).

Thus, Kay et al. anticipate claims 1 and 7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 9, 10, 11, 12, 13, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wianny et al. (Nature Cell Biology, 2000 Vol. 2:70-75) in view of Caplen et al. (Proc Natl Acad Sci, 2001 Vol. 98:9742-7, Epub 2001 Jul 31).

Claim 1 is drawn to a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression, comprising making a polynucleotide that is complementary to a nucleic acid sequence, inserting the polynucleotide into a vessel and delivering the polynucleotide to the cell. Claim 1 is drawn to a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression, comprising making a polynucleotide that is

complementary to a nucleic acid sequence, inserting the polynucleotide into a vessel and delivering the polynucleotide to the cell. Claims 3-5, 9, 10, 13, 14, and 15 are dependent on claim 1 and include all the limitations of claim 1 and provide the further limitations, wherein vessel permeability is increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, and wherein the pressure increases extravascular volume. Claims 11 and 12 are dependent on claim 1 and include all the limitations of claim 1 and provide the further limitation, wherein the polynucleotide consists of siRNA and wherein the siRNA is injected into the mammal's vessel.

Wianny et al. disclose long dsRNAs diluted in water and microinjected into the cytoplasm of oocytes and embryos of mice (see page 74, first and second columns, for example). Wianny et al. further disclose that some blastocytes derived from zygotes injected with dsRNAs were transferred into the uteri of pseudopregnant mice (see page 74, second column, for example and page 72, first column).

The term "vessel" is interpreted broadly such that transferring the zygotes injected with dsRNA into the uteri is equivalent to inserting the polynucleotide into a vessel as claimed. Transferring the zygotes injected with dsRNA into the uteri is equivalent to increasing vessel permeability, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, increasing extravascular volume, and organ volume as claimed because the method of transferring the zygotes injected with dsRNA into the uteri would inherently increase pressure in the area of microinjection and at the time of transferring. The pressure against the vessel walls would inherently be increased because the microinjection needle used is external to the uteri and

injecting an increased volume of solution into the uteri would increase volume and pressure against the vessel walls.

Wianny et al. do not teach delivering siRNA into a cell to inhibit protein expression.

Caplen et al. teach the specific inhibition of gene expression by small double-stranded RNAs (siRNA) in invertebrate and vertebrate systems. Caplen et al. further teach that long double-stranded RNAs exhibit nonspecific effects on gene expression in mammalian cells and vertebrate systems. Caplen et al. further teach that these nonspecific responses are mostly due to the activation of PKC. Caplen et al. teach that PKR activation is dependent on double-stranded RNA length and double-stranded RNA less than 30 nucleotides are unable to activate PKR, thus resulting in gene-specific RNAi response in model invertebrates and mammalian cells (see page 9742, second column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use small double-stranded RNAs taught by Caplen et al. to inhibit protein expression in a mammal as taught by Wianny et al. One of ordinary skill in the art would have been motivated to use siRNA because these nucleotides do not activate PKR and exhibit more gene-specific RNAi responses. Thus one of ordinary skill in the art would have been motivated to make and use siRNA over long double-stranded RNA, in order to overcome the nonspecific effects/responses exhibited by long double-stranded RNA.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
June 1, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER